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Tumour Review

Progress in the knowledge and treatment of advanced pancreatic cancer: From benchside to bedside

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ABSTRACT

Ever since a pivotal study in 1997 demonstrated superiority of gemcitabine over 5-FU, gemcitabine monotherapy has, until recently, comprised the standard of care in patients with advanced pancreatic cancer. However, the emerging recognition of the pancreatic cancer microenvironment, including the particularly abundant stroma, as playing a key role in disease progression and resistance to chemotherapy has marked somewhat of a paradigm shift in the way treatment of advanced pancreatic cancer is viewed, with these very same biological defenses conversely offering an Achilles heel with which to combat this aggressive disease. Recently, this approach was validated for the first time in a pivotal phase III trial in which patients received nab-paclitaxel, a stroma-targeted drug, with gemcitabine. Overall survival was significantly ($p < 0.001$) prolonged in the combination arm, compared with gemcitabine alone, and thus these convincing results pave the way forward for future treatment regimens that employ a multipronged approach, targeting not only the primary tumor but the surrounding microenvironment as well.

Introduction

Of all the solid tumors, pancreatic cancer carries one of the most dismal prognoses, with a median overall survival duration of approximately 6 months following diagnosis and an overall survival rate at 5 years of less than 5% [1]. Reasons for this include marked tumor resistance to chemotherapy and radiotherapy, lack of specific early symptoms resulting in advanced disease upon diagnosis and the ability of pancreatic cancer cells to metastasize early in disease development [2]. Indeed, for the approximately 15–20% of patients with seemingly operable disease at presentation, micrometastases have usually already been established [3] and 85% of these patients will eventually experience relapse and subsequent cancer-related death [4]. However, the majority of patients are diagnosed at a late stage in disease development, with approximately 30% and 50% having locally-advanced unresectable and metastatic disease, respectively, upon presentation [5].

Currently, definitive risk factors for pancreatic cancer remain largely unknown. Of several environmental agents possibly associated with increased risk, only tobacco use has been established as having a causative role, with smokers experiencing a 2.5–3.6-fold higher risk of disease [1]. Other possible environmental causes are nitrites which are used as preservatives in processed meats [6]. Overweight or obesity was confirmed as a risk factor in a large case-control study in which it was shown that subjects who were overweight from 14 to 39 years of age or who were obese from 20 to 49 years of age had a statistically significant increased risk of pancreatic cancer (highest odds ratios of 1.67 [95%CI: 1.20–2.34] and 2.58 [95%CI: 1.70–3.90], respectively), regardless of whether or not they had concomitant diabetes mellitus, another possible risk factor. Additionally, overweight or obesity resulted in earlier onset of disease [7].

Diabetes is associated with pancreatic cancer but whether or not it is a causative factor, an effect due to pancreatic cancer or both has yet to definitively determined. In a population-based cohort study conducted in Taiwanese patients, diabetes mellitus for less than 2 years was found to be significantly correlated with increased risk of pancreatic cancer, with the incidence being approximately 4 times higher than that observed in non-diabetic patients (27.81 vs. 6.96 cases per 10,000 patient-years). However, an increased risk of pancreatic cancer was not found in patients with long-term diabetes [8].

Familial mutations are important risk factors for pancreatic cancer, with 7–10% of pancreatic cancer patients having a family history of this disease. A first-degree relative of an individual with familial pancreatic cancer has a 9-fold higher risk of developing this neoplasm and those with 3 or more affected first-degree relatives have a 32-fold higher risk. Moreover, familial pancreatic

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cancer is associated with an increased incidence of precancerous lesions and extra-pancreatic malignancies.

Other possible risk factors that have yet to be validated include a high-fat diet or a diet that contains few vegetables, non 'O' blood type, African-American ethnicity, older age and male gender [9].

Treatment for early-stage pancreatic cancer comprises surgery followed by adjuvant chemotherapy which is usually gemcitabine or 5-FU (fluorouracil) [10]. Recently, a long-term analysis was published of the pivotal CONKO-001 study which compared adjuvant gemcitabine with observation alone in patients with resected pancreatic cancer. After a median follow-up period of 11.3 years, disease-free survival, the primary endpoint, was significantly longer in the gemcitabine arm (median of 13.4 vs. 6.7 months; $p < 0.001$) as was survival (median of 22.8 months vs. 20.2 months; $p = 0.01$). Moreover, the 5-year overall survival of 20.7% vs. 10.4% and 10-year overall survival of 12.2% vs. 7.7% was prolonged [11].

With respect to administration of neoadjuvant therapy, results so far have been inconclusive in patients with primarily resectable disease [10]. In patients with borderline resectable/unresectable pancreatic cancer, administration of chemotherapy may increase the chance of resection and, consequently, improve survival outcomes [12]. Regarding the value of radiotherapy in the treatment of locally advanced pancreatic cancer, addition of radiotherapy is not superior to continuing chemotherapy after four months of induction therapy, with the final results of the international phase III LAP 07 study showing no significant differences in efficacy between chemotherapy and chemoradiotherapy arms [13].

Unfortunately, due to the majority of patients presenting with disease that is already unresectable and/or metastatic, treatment is usually palliative, with the main goals being to ameliorate symptoms and extend survival.

Ever since gemcitabine was confirmed as the standard of care for advanced pancreatic cancer in 1997 [14], progress in improving survival outcomes has been painfully slow, with many different gemcitabine-based combinations demonstrating no more efficacy than gemcitabine alone, aside from when administered in patients with good performance status [15].

Regarding predictive biomarkers for pancreatic cancer treatment, human equilibrative nucleoside transporter 1 (hENT-1) has been identified as a predictor of response to gemcitabine. A multivariate analysis of the ESPAC-1 and -3 trials showed that increased intratumoral hENT-1 was significantly correlated to response to gemcitabine ($p = 0.008$) but not fluorouracil [16]. Similar outcomes were seen in another multivariate analysis of the RTOG 9704 trial, in which higher hENT-1 levels in gemcitabine recipients were associated with significantly ($p = 0.018$) longer overall survival, compared with those patients with lower hENT-1 levels (median of 24.2 vs. 14.8 months) [17]. Presently, a phase II trial (NCT01726582) is being conducted in patients with borderline resectable/unresectable pancreatic cancer which is assessing 6 biomarkers considered to be predictive of treatment response-secreted protein acidic and rich in cysteine (SPARC; nab-paclitaxel), ribonucleotide reductase M1 (RRM1; gemcitabine), excision repair cross-complementation group 1 (ERCC1; platinum analogs), topoisomerase 1 (TOPO1; irinotecan), hENT-1 (gemcitabine) and TYMS (fluorouracil) [18].

Genetics

Over the last decade our understanding of pancreatic cancer genetics has increased substantially, with a number of germline and somatic mutations being identified and mapped. KRAS-activating mutations, a somatic mutation found in approximately 90% of pancreatic cancers, and its downstream signaling pathways MAPK and PI3K have been the focus of intense efforts to develop targeted therapies [19]. Unfortunately, success so far has been thwarted due to the difficulty in developing a protein that precisely matches the active site in the KRAS protein. As KRAS only becomes fully activated once it is transported and embedded in the cell membrane, a new approach has been taken in which KRAS itself is not targeted but instead the target is its transport protein PDE-δ. Preclinical results appear promising thus far but have yet to be validated in clinical trials [20].

Other common somatic mutations in pancreatic cancer include inactivation of tumor suppressor genes such as CDKN2A, BRCA2, TP53 and SMAD4, with the latter three mutations occurring in advanced-stage disease. Epigenetic dysregulation is also implicated in the pathogenesis of pancreatic cancer and in neoplasms without genetic inactivation of tumor suppressor genes, gene silencing can occur via promoter methylation [9]. Currently, a demethylation agent, azacitidine, is being assessed in combination with gemcitabine in a phase I clinical trial in 30 patients with advanced disease (NCT01167816) and trial completion is scheduled for July 2014.

It is also becoming clear that pancreatic cancer tumors are highly heterogeneous, with results from a global landmark genomic analysis of 24 advanced pancreatic adenocarcinomas showing that tumors contain on average 63 genetic alterations. This heterogeneity may partially explain the notorious resistance of pancreatic cancer to chemotherapy and, unfortunately, it may also render the idea of targeted therapies to specific tumor mutations as largely unrealistic [21].

The pancreatic cancer microenvironment

Epithelial-mesenchymal transition

Characterized by multiple biochemical changes resulting in loss of cell polarity and transformation of an epithelial cell into a mesenchymal cell phenotype, the epithelial-mesenchymal transition (EMT) is a pivotal process in tumor progression. EMT enables cancer cells to become unanchored from the primary tumor and to subsequently disseminate into the bloodstream [22], thus initiating the first steps in the establishment of micrometastases and the ability of pancreatic cancer to undergo this process at a particularly early stage in disease development is one of the major reasons for its dismal prognosis [23]. Tumor growth factor-beta (TGF-ß) is one of the key induction agents of EMT [24], as well as being a mediator of fibrosis within the stroma. Recently, trabedersen, an inhibitor of TGF-ß receptor-2, demonstrated activity in a phase I trial in patients with advanced TGF-ß overexpressing solid tumors, with a median overall survival duration of 9.2 months being observed in the subgroup of patients with pancreatic cancer [25].

As well as contributing to disease progression, EMT also plays a role in the development of drug resistance. In a recent study which aimed to characterize the resistance of pancreatic cancer cell lines to 3 different classes of cytotoxic chemotherapy (gemcitabine, 5-FU and cisplatin), high levels of transcriptional factor Zeb-1, an EMT activator, and low levels of E-cadherin, a cell adhesion protein, were associated with increased resistance to all 3 drugs; subsequent silencing of Zeb1 increased E-cadherin levels and restored drug sensitivity [26]. Similar results have been observed with targeted biologics as well [27]. Inhibition of Notch-2 has been found to downregulate Zeb1 expression and recently a clinical trial was conducted that assessed the preliminary efficacy and pharmacodynamic effects of a notch signaling pathway inhibitor, RO4929097 (RG-4733), in patients with metastatic disease (NCT01232829). However, results from this trial have yet to be published.

Immune evasion

As a result of genomic instability and inappropriate gene expression, tumor cells express antigens that differentiate them from normal cells and thus provide potential targets for recognition by the immune system. However, although many types of immune cells are associated with tumor suppression, such as tumor-infiltrating lymphocytes, tumor-promoting roles have been identified in cells such as myeloid-derived suppressor cells, tumor-associated macrophages and B-cells [28]. Due to the tumor microenvironment being chronically inflamed, immunosuppressive cells, such as macrophages and regulatory T-cells, are recruited to the stroma, resulting in a decrease in antitumor immunity which is more pronounced in pancreatic cancer, compared with other solid tumors [29].

CD40, a tumor necrosis factor-receptor super family member, has emerged as an attractive therapeutic target due to its central role in mediating antitumor immunity [30]. In the first part of a study conducted in 2011, treatment-naïve patients with advanced unresectable pancreatic cancer were treated with a fully human agonist CD40 monoclonal antibody, CP-870, 893 as well as gemcitabine. Of the 21 patients, 19% had a partial response, 52% had stable disease and treatment was well tolerated. Similar results were subsequently demonstrated with administration of CD40 agonist FGK45 plus gemcitabine in a murine model which replicated the tumor stroma (*Kras*$^{LSL\text{-}G12D/+}$;*Trp53*$^{LSL\text{-}R172H/+}$;*Cre* [KPC] mice), with tumor regression being observed in 30% of mice. Interestingly, the activity of FGK45 in KPC mice did not appear to be dependent on the presence of T-cells or gemcitabine but did require macrophages, with CD40-activated macrophages being shown to rapidly infiltrate tumors where they transformed into tumoricidal cells, facilitating depletion of the tumor stroma [29].

The pancreatic cancer stroma

Overview

Formed as a result of a desmoplastic reaction, the stroma has recently emerged as a key mediator of pancreatic cancer growth and invasion as well as being a major factor in the notable resistance pancreatic cancer to chemotherapy. This is in contrast to earlier views of the stroma functioning merely as a mechanical protective barrier for the benefit of the host [31]. It is now recognized that the stroma functions as a dynamic interface between the tumor and normal host epithelial tissue and comprises compact fibrous tissue as well as cells such as pancreatic stellate cells/cancer-associated stromal fibroblasts, endothelial cells, immune cells and tumor cells as well as extracellular matrix (ECM) proteins and growth factors [32]. Moreover, compared with other solid tumors, the pancreatic cancer stroma is particularly dense and abundant, comprising up to 90% of tumor volume [31]. Consequently, it has been one of the major obstacles in drug development for pancreatic cancer due to the difficulty in replicating it in preclinical models and, as a result, drugs that initially appear promising often fail in subsequent clinical trials. However, it is now becoming clear that in order to elicit a meaningful response and improve patient survival, treating the primary tumor in pancreatic cancer is not enough – the tumor stroma must be targeted as well.

Pancreatic stellate cells/cancer-associated stromal fibroblasts

Pancreatic stellate cells are considered to be the principal regulators of stromal formation and turnover. Upon activation from their usual quiescent state by various cytokines and growth factors as well as oxidative stress, they transform into myofibroblast-like cells, secreting large amounts of ECM proteins and growth factors, resulting in increased proliferation of tumor cells. Moreover, the accumulation of ECM proteins into periacinar spaces as well as the unchecked increase in levels of pancreatic stellate cells distorts the normal parenchymal structure of the tumor. This results in increased interstitial pressure, subsequent capillary compression and impaired blood perfusion which hinders delivery of chemotherapy as well as oxygen diffusion. This induced hypoxic state also promotes tumor cell survival, progression, invasion and metastasis via activation of a range of genes by hypoxia-inducible factor 1-α and induces EMT [33], contributing further to chemoresistance. Due to playing such a central role in stroma development, tumor progression and chemoresistance, pancreatic stellate cells are therefore considered to be an attractive therapeutic target.

Platelet-derived growth factor (PDGF) is a powerful chemoattractant for pancreatic stellate cells [34] and also functions as a promoter of pancreatic stellate cell proliferation. It was hypothesized that inhibition of PDGF signaling could decrease levels of pancreatic stellate cells, leading to reduced intratumoral interstitial pressure and, consequently, increased uptake of chemotherapy. This hypothesis was confirmed in preclinical trials, including one in which co-administration of imatinib, a PDGF receptor inhibitor, with gemcitabine resulted in a tumor sized 36% smaller than the tumor treated with gemcitabine alone [35]. Unfortunately, a recently completed phase II study showed no difference in progression-free survival or overall survival between the imatinib plus gemcitabine and gemcitabine alone arms [36].

Hyaluronic acid

Another component of the stroma which is present in high levels is hyaluronic acid. Within the stroma, hyaluronic acid levels are a major determinant of elevated interstitial fluid pressures and administration of hyaluronidase in KPC mice resulted in normalization of interstitial fluid pressure and, consequently, a significant increase in the diameters of CD31 + vessels. A subsequent preclinical trial in KPC mice compared gemcitabine plus hyaluronidase vs. gemcitabine alone. Of the evaluable tumors, 83% of gemcitabine plus hyaluronidase-treated tumors had an objective clinical response whereas no responses were observed in the gemcitabine plus placebo-treated tumors [37]. Unfortunately, this success was not replicated in a subsequent phase I/II clinical trial [38]. In a randomized open-label phase II trial, gemcitabine plus nab-paclitaxel plus hyaluronidase is being compared with gemcitabine plus nab-paclitaxel alone (NCT01839487). The primary endpoint is progression-free survival and completion is scheduled for September 2015.

Sonic hedgehog pathway

Recently it was observed that cancer-associated stromal fibroblasts overexpress the Hedgehog receptor smoothened (SMO), leading to inappropriate activation and deregulation of the Sonic Hedgehog (SHH) pathway, a key signaling pathway in embryogenesis and a prominent characteristic of pancreatic cancer [39]. As a result of these findings, inhibition of the SMO receptor was investigated in several preclinical studies. In one study, administration of gemcitabine with the SMO receptor inhibitor saridegib in gemcitabine-resistant KPC mice resulted in increased tumor vasculature, a higher intratumoral gemcitabine concentration and extended overall survival [40]. Similar findings were observed in other preclinical studies. However, although these data provided a strong rationale for investigating inhibition of the SHH pathway in a clinical setting, results so far have been disappointing [41,42]. Once again, translation of preclinical results into meaningful clinical improvements in pancreatic cancer patients proved more difficult than expected.

SPARC

As well as the SMO receptor, cancer-associated stromal fibroblasts also overexpress the SPARC protein. SPARC is also found in approximately 80% of pancreatic adenocarcinomas [30] but the promoter is often silenced in tumor cells via hypermethylation [43]. However, SPARC in the stroma is active and high levels are associated with a poor prognosis [44]. SPARC belongs to the matricellular class of proteins and functions predominantly as a regulator of tissue remodeling, including influencing the deposition and composition of the ECM. Additionally, SPARC decreases the activation threshold of specific growth factors by increasing complex formation of growth factors and enhancing cross-talk between integrins and growth factor receptors. Therefore, it would appear that SPARC plays a key role in the tumor-ECM interface and, consequently in tumor proliferation, invasion, metastasis and survival [43].

One of the first observations leading to identification of this protein was its binding affinity to albumin. SPARC mediates accumulation of albumin in the tumor which is then thought to be used for nutrition as well as a nitrogen source to synthesize new proteins. It is hypothesized that nab-paclitaxel, which comprises albumin-bound paclitaxel, takes advantage of this particular action of SPARC as well as other albumin-dependent processes [45]. However, data to confirm this hypothesis are still pending. In a preclinical component of a recent phase II study, co-administration of nab-paclitaxel plus gemcitabine in 11 patient-derived pancreatic cancer xenografts resulted in a higher tumor regression rate than either agent alone with aggregate regression rates of 55%, 36% and 24% in murine models of pancreatic cancer receiving nab-paclitaxel plus gemcitabine, nab-paclitaxel alone and gemcitabine alone, respectively (Fig. 1). Additionally, greater stromal depletion and vascularity were observed with the combination, compared to either monotherapy, and the intratumoural gemcitabine concentration was 2.8 times higher than that observed with gemcitabine alone. In the clinical part of the trial, co-administration of the maximum tolerated dose of gemcitabine with nab-paclitaxel in patients with advanced pancreatic cancer resulted in an objective response rate of 48%, a median overall survival duration of 12.2 months and a 1-year survival rate of 48% [46]. These promising clinical results were recently validated in the pivotal phase III MPACT clinical trial [47,48], thus making nab-paclitaxel the first drug hypothesized to target the stroma to reach this milestone so far.

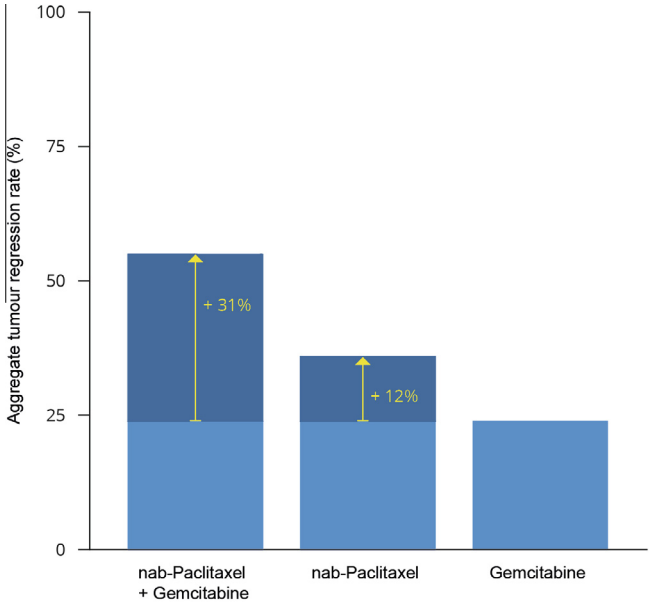

Fig. 1. Percentage incidence of aggregate tumor regression in response to gemcitabine, nab-paclitaxel and gemcitabine plus nab-paclitaxel in mice xenografts [46].

Another proposed mechanism for the increased accumulation of nab-paclitaxel, compared with standard paclitaxel, is its enhanced transport across endothelial cells. This is thought to occur via binding of the albumin-paclitaxel complex to the gp60 albumin receptor on the surface of endothelial cells following drug dissolution, leading to caveolae formation and subsequent caveolin-1 mediated transcytosis of the vesicles through the endothelial cell where they are subsequently emptied into the subendothelial space. Once inside the subendothelial space, nab-paclitaxel seems to bind to various extracellular matrix proteins, including SPARC, and is then taken up by the tumor [49].

Nab-paclitaxel vs. standard paclitaxel

In addition to its possible affinity to SPARC, the high intratumoural concentration of nab-paclitaxel is thought to be due to pharmacokinetics, with nab-paclitaxel demonstrating a peak drug concentration of free paclitaxel that is approximately 10 times higher than that of standard paclitaxel (1283.7 vs. 121.79 ng/mL; $p < 0.000001$), and an AUC that is approximately 3 times higher (1159 vs. 410 h*ng/mL; $p < 0.000005$) when both drugs are administered at approved doses. Moreover, nab-paclitaxel also demonstrates dose exposure/linearity over a clinically relevant dose range whereas, due to micellar encapsulation by the solvent polyoxyl-35 castor oil, standard paclitaxel demonstrates limited drug distribution and clearance and, consequently, nonlinear pharmacokinetics [50]. Another benefit of not requiring polyoxyl-35 castor oil for dissolution is improved tolerability, compared with standard paclitaxel [51].

Pancreatic mast cells

Mast cells promote proliferation of pancreatic stellate cells within the desmoplastic environment via production of interleukin-13 and tryptase, thus rendering them a promising target for the inhibition of stromal formation [52]. In a phase III trial, chemo-naïve pancreatic cancer patients ($n = 348$) received the selective mast/stem cell growth factor receptor (c-Kit) inhibitor masitinib [53], in combination with gemcitabine. A significant survival advantage over gemcitabine monotherapy was observed in the subgroups of patients with "pain" (8.1 vs. 5.4 months) and the prognostic biomarker GBM (11.0 vs. 5.0 months), but not in the overall patient population [53].

Inhibition of Janus kinases

The STAT protein (Signal Transducer and Activator of Transcription) is responsible for many major cell functions, such as growth, survival and differentiation, and is activated by Janus kinase (JAK) [54]. Activation of the JAK/STAT pathway plays a role in many conditions such as inflammatory diseases and cancer. Ruxolitinib is an oral JAK1 and JAK2 inhibitor that has recently been approved for the treatment of myelofibrosis and has also been tested against different solid tumours, including pancreatic cancer [54]. Results from a phase II study of ruxolitinib in combination with capecitabine resulted in a hazard ratio for overall survival of 0.47 in a subgroup of pancreatic cancer patients with C-reactive protein levels that were higher than the treatment arm median of 13 mg/L. In this same subgroup, the 3- and 6-month survival rates were 48% and 42%, compared to 29% and 11% in the capecitabine monotherapy group, respectively [55].

Pivotal clinical trials of first-line therapies in patients with advanced pancreatic cancer

Gemcitabine vs. fluorouracil

Gemcitabine monotherapy has been the standard of care for advanced pancreatic cancer since 1997 when a pivotal study by Burris et al., demonstrated superiority of gemcitabine over 5-FU (Tables 1–4). The primary endpoint of this study was clinical benefit response, a composite of pain intensity, analgesic consumption, bodyweight and Karnofsky performance status, with survival being a secondary outcome. As compared to 5-FU, gemcitabine resulted in a significantly higher proportion of patients experiencing a clinical benefit response (23.8% vs. 4.8%; $p = 0.0022$), as well as a significantly higher 1-year survival rate (18% vs. 2% of patients) and a significantly longer survival duration (median of 5.65 vs. 4.41 months; $p = 0.0025$). Both treatments were generally well tolerated with rates of hematological and non-hematological adverse events being low and usually of a mild severity. However, gemcitabine was associated with non-significantly higher rates of grade 3 or 4 nausea/vomiting and anemia (12.7% vs. 4.8% and 9.7% vs. 0% of patients, respectively) and a significantly higher rate of grade 3 or 4 neutropenia (25.9% vs. 4.9% of patients; $p < 0.001$) [14].

Erlotinib plus gemcitabine vs. gemcitabine alone: the PA.3 trial

Targeted therapies have generally proven disappointing in clinical trials of patients with pancreatic cancer, despite demonstrating efficacy in other solid malignancies. The only phase III trial to show a significant improvement in survival was the multinational PA.3 trial, comparing erlotinib plus gemcitabine with gemcitabine alone (Tables 1–4). The increase in survival in the erlotinib plus gemcitabine arm was significant but modest (median of 6.24 vs. 5.91 months; hazard ratio 0.82, 95% CI 0.69, 0.99). Erlotinib plus gemcitabine was associated with higher rates of diarrhea, rash, stomatitis and infection although most of these were only grade 1 or 2 in severity. As previously observed in other studies, appearance of a rash was significantly correlated with improved disease control ($p = 0.05$) as well as survival, with erlotinib recipients experiencing a grade 2 or higher rash living significantly longer than those patients with no rash or a grade 1 rash (median of 10.5 vs. 5.3 and 5.8 months, respectively; $p < 0.001$). However, only 36% of erlotinib plus gemcitabine recipients developed a rash of grade 2 or higher and overall survival in the majority of erlotinib plus gemcitabine recipients was similar to gemcitabine alone [56]. Therefore, due to the increase in survival being so small in the general patient population, erlotinib has not been broadly adopted by oncologists as part of standard of care.

FOLFIRINOX vs. gemcitabine: the ACCORD-4 trial

A multicenter phase III trial in France was completed in 2010 in which a median survival duration of 11.1 months was achieved for the first time in patients with metastatic pancreatic cancer. The treatment regimen administered was FOLFIRINOX with the comparator arm (gemcitabine monotherapy) resulting in a significantly shorter median survival duration (6.8 months; primary endpoint) (Tables 1–4). FOLFIRINOX was also associated with a significantly longer progression-free survival interval (median of 6.4 vs. 3.3 months; $p < 0.001$) and a significantly higher objective clinical response rate (31.6% vs. 9.4% in the intention-to-treat population; $p < 0.001$). Furthermore, time to definitive deterioration in quality of life, with respect to function and symptom scale scores as well as constipation, dyspnea and loss of appetite, was significantly prolonged in the FOLFIRINOX arm, compared with gemcitabine alone. Unfortunately, the greater efficacy of FOLFIRINOX was accompanied by a substantial increase in toxicity; in particular grade 3/4 diarrhea, sensory neuropathy, neutropenia and febrile neutropenia ($p < 0.001$, $p < 0.001$, $p < 0.001$ and $p < 0.05$, respectively, vs. gemcitabine alone) [57]. The study also contained strict inclusion criteria-patients had to be younger than 76 years of age, have an ECOG performance status of no more than 1 as well as no cardiac ischemia. Moreover, due to an increased risk of irinotecan-associated toxicity, only patients with good hepatobiliary function were enrolled and, as a result, the distribution of pancreatic tumor location was the opposite to what would normally be seen in clinical practice, with approximately 60% of patients having non-head tumors of the pancreas and, consequently, only 14% of patients had an endobiliary stent [58]. In normal clinical practice, a ratio of 3:1 for head lesions vs. body or tail lesions is usually observed [59]. As the risk of ascending cholangitis and biliary sepsis is higher in patients with obstructing pancreatic head lesions and indwelling biliary stents, the increased likelihood of grade 3/4 neutropenia associated with the FOLFIRINOX regimen could result in potentially life-threatening situations. This would be especially serious in centers with limited or no access to specialists in endoscopic management of biliary complications [58]. However, it is not certain whether all components of FOLFIRINOX are necessary and modified regimens are currently being evaluated. A retrospective study investigated a modified FOLFIRINOX regimen in which the fluorouracil bolus was omitted and prophylactic growth factor was added. Results were promising, with the modified regimen appearing to be well tolerated, although it needs to be validated in a prospectively planned clinical trial [60].

Therefore, although FOLFIRINOX is an effective regimen, thus far it is unsuitable for many patients due to its toxicity and as a result its clinical impact is thought to be modest.

Nab-paclitaxel + gemcitabine vs. gemcitabine alone: the MPACT trial

In November 2012, the primary endpoint was met in the pivotal phase III multinational MPACT trial, with nab-paclitaxel plus gemcitabine demonstrating significantly longer overall survival than gemcitabine alone (median duration of 8.7 vs. 6.6 months; hazard ratio 0.72; 95% CI 0.620, 0.825; updated cutoff May 9th 2013) in patients with metastatic pancreatic cancer (Tables 1–4). This

Table 1
Pivotal phase III trials in patients with advanced disease. Bold values symbolize the treatment of interest.

	Number of patients	Treatment
[14]	126	**Gemcitabine** (1000 mg/m^2 weekly × 7, 1 week arrest, then weekly × 3 every 4 weeks) vs. 5-FU (600 mg/m^2 once weekly)
[56]	569	**Gemcitabine** (standard) + **erlotinib** (100 or 150 mg/d orally) vs. Gemcitabine + placebo
[57]	342	**FOLFIRINOX** (oxaliplatin, 85 mg/m^2; irinotecan, 180 mg/m^2; leucovorin, 400 mg/m^2; and fluorouracil, 400 mg/m^2 bolus followed by 2400 mg/m^2 46-h continuous infusion every 2 weeks) vs. gemcitabine (1000 mg/m^2 weekly for 7 of 8 weeks, then weekly for 3 of 4 weeks)
[48]	861	**NABPAC** (125 mg/m^2 followed by gemcitabine 1000 mg/m^2 on days 1, 8, and 15 every 4 weeks) vs. gemcitabine (1000 mg/m^2 weekly for 7 of 8 weeks and on days 1, 8, and 15 every 4 weeks)

Table 2
Patient demographics in pivotal phase III trials in patients with advanced disease.

	[14] GEM	[56] GEM/ERL	[57] FOLFIRINOX	[48] NABPAC
Age (range)	62 (37–79)	63.7 (37–84)	61 (25–76)	62 (27–88)
Performance status	30% KPS 80–90 70% KPS 50–70	29.8% ECOG 0 50.9% ECOG 1 18.9% ECOG 2	37.4% ECOG 0 61.9% ECOG 1 0.6% ECOG 2	16% KPS 100 77% KPS 80–90 7% KPS 60–70
Liver metastases	NR	NR	87.6%	85%
Head of pancreas	NR	NR	39.2%	44%
CA19.9 ⩾ 59 ULN	NR	NR	41.5%	52%

GEM, gemcitabine; ERL, erlotinib; FOLFIRINOX, folinic acid + fluorouracil + irinotecan + oxaliplatin; NABPAC, nab-paclitaxel; KPS, Karnofsky performance status; ECOG, Eastern Cooperative Oncology Group performance status; ULN, upper limit of normal; NR, not reported.

Table 3
Clinical outcomes in pivotal phase III trials in patients with advanced disease.

	[14] GEM	[56] GEM/ERL	[57] FOLFIRINOX	[48] NABPAC
OS (median months)	5.65 $p = 0.0025$	6.24 $p = 0.038$	11.1 $p = 0.001$	8.7 $p < 0.001$
12-month OS (% patients)	18	23	48.4	35
18-month OS (% patients)	NR	NR	18.6	16
ORR (% patients)	5.4	8.6	31.6	29.2

ORR, overall response rate; OS, overall survival; GEM, gemcitabine; ERL, erlotinib; FOLFIRINOX, folinic acid + fluorouracil + irinotecan + oxaliplatin; NABPAC, nab-paclitaxel.

Table 4
Grade 3 or higher adverse events (% patients) in pivotal phase III trials.

	[14] GEM	[56] GEM/ERL	[57] FOLFIRINOX	[48] GEM/NABPAC
Neutropenia	25.9	24	45.7	38
Febrile neutropenia	NR	NR	5.4	3
Thrombocytopenia	9.7	10	9.1	13
Fatigue	NR	15	23.6	17
Diarrhea	1.6	6	12.7	6
Peripheral neuropathy	NR	NR	9.0	17[a]

GEM, gemcitabine; ERL, erlotinib; FOLFIRINOX, folinic acid + fluorouracil + irinotecan + oxaliplatin; NABPAC, nab-paclitaxel; NR, not reported.
[a] Grade ⩾ 3 neuropathy improved to no more than grade 1 in a median of 29 days.

improvement in overall survival was observed across almost all patient subgroups, with the patients who had more advanced disease deriving the greatest benefit from the nab-paclitaxel plus gemcitabine combination. In particular, patients with more than 3 metastatic sites, a Karnofsky performance status of 70–80, presence of liver metastases or a CA19-9 level which was 59 times the upper limit of normal or higher had the greatest reduction in the risk of death.

Other significantly improved endpoints included progression-free survival (median interval of 5.5 vs. 3.7 months; $p < 0.001$) and objective response (complete plus partial response) (29% vs. 8% in the intention-to-treat population; $p < 0.001$). Moreover, the 1-year survival rate was significantly higher in the nab-paclitaxel arm plus gemcitabine, compared with gemcitabine alone (35% vs. 22% in the intention-to-treat population; $p < 0.001$), as was the 2-year survival rate in the intention-to-treat population. The response rate according to independent review was 23% in the nab-paclitaxel group versus 7% in the comparator arm ($p < 0.001$). With respect to tolerability, nab-paclitaxel plus gemcitabine was associated with increased but manageable toxicity, with the most frequently reported grade 3 or higher adverse events being neutropenia (38% vs. 27% of patients), leukopenia (31% vs. 16% of patients), fatigue (17% vs. 7% of patients) and neuropathy (17% vs. 1% of patients). However, median times to decrease from grade 3 to either grade 2 neuropathy or neuropathy of grade 1 or lower were relatively short (21 and 29 days, respectively) [47,48].

Therefore, due to resulting in a substantially longer overall survival duration, compared with standard of care, as well as being associated with a manageable increase in toxicity, nab-paclitaxel plus gemcitabine can be considered to be an important new regimen in the treatment of advanced pancreatic cancer.

Is nab-paclitaxel + gemcitabine a new treatment standard?

Although inter-study comparisons of pivotal trials are inherently limited, they can nevertheless provide a useful overview of current treatment landscapes. Nab-paclitaxel plus gemcitabine resulted in a substantially longer median overall survival duration than the gemcitabine monotherapy arm in the 1997 study by Burris et al., as well as the erlotinib plus gemcitabine arm in the PA.3 trial (8.5 vs. 5.65 vs. 6.24 months, respectively) and was associated with less toxicity than the FOLFIRINOX regimen, particularly with respect to neutropenia. Furthermore, the MPACT trial differed from the FOLFIRINOX trial in several important aspects, including allowing patients to enroll with an ECOG performance status of 2 as well as enrolling patients 75 years or older. In fact, 10% of the patient

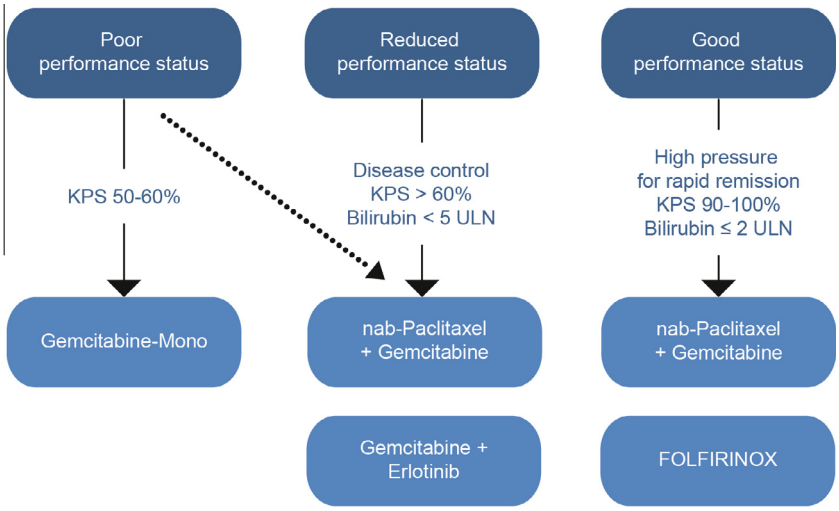

Fig. 2. Treatment algorithm for advanced metastatic pancreatic cancer.

population in the MPACT trial were at least 75 years of age and 8% had a KPS of 60–70%, equivalent to an ECOG of 2 [48].

As a result of the positive data from the MPACT trial, the National Cancer Association Network updated its guidelines for the treatment of pancreatic cancer in April 2013, with nab-paclitaxel plus gemcitabine being moved from a category 2B to a category 1 listing, defined as being "based on high-level evidence, there is uniform NCCN consensus that the intervention is appropriate" [61].

Additionally, following a Priority Review granted by the FDA in May 2013 [62], nab-paclitaxel received approval in September 2013 to be administered in combination with gemcitabine as first-line therapy for metastatic pancreatic cancer [63], thus making it the first drug to be approved for advanced pancreatic cancer in nearly 8 years. Furthermore, EMA approval was granted in December 2013. Nab-paclitaxel plus gemcitabine should therefore be considered as an eminent therapeutic option in patients with advanced pancreatic cancer, administered either alone or as a backbone in other treatment regimens.

Conclusion

Although progress has been made in the treatment of advanced pancreatic cancer in the last 15 years, it is clear that new strategies are needed if patients' lives are to be substantially prolonged and it is becoming clear that targeting the primary tumor alone is inadequate in this most resilient of malignancies. The relatively recent discovery that the tumor microenvironment is a key player in tumor progression and metastasis as well as immune evasion and moreover, that the stroma is a major factor in the notable drug resistance of pancreatic cancer, has initiated somewhat of a paradigm shift in the way pancreatic cancer and its treatment are viewed. Novel regimens in which a multi-faceted approach is undertaken, targeting not only the primary tumor, but also the surrounding structures such as the tumor stroma, are starting to be investigated, with the hope of increasing response rates and, consequently, survival. Many early-phase studies of these multitargeted regimens are now active and their results are eagerly awaited by the oncology community.

Nab-paclitaxel plus gemcitabine is the first of such regimens to be validated in a phase III setting in patients with metastatic pancreatic cancer. This combination demonstrated a significantly greater improvement in the hard endpoint of overall survival when compared with the reference regimen of gemcitabine alone and as a result it joins the growing armamentarium against this challenging disease. A treatment algorithm for patients with advanced metastatic pancreatic cancer is given in Fig. 2. As our understanding of pancreatic cancer biology grows, so too does the likelihood of being able to implement therapeutic regimens in real-life settings that result in meaningful improvements in survival and quality-of-life outcomes accompanied by acceptable tolerability. Hopefully, the recent success observed with nab-paclitaxel marks the beginning of a new era in the treatment of advanced metastatic pancreatic cancer.

Conflict of interest

Helmut Oettle has received consulting fees from Celgene, Lilly, and Roche. He has received financial support for research projects from Bayer, Celgene, Roche, and Lilly.

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